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17 March 2005

For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.

(54) Title: METHODS AND COMPOSITIONS TARGETING TYROSINE KINASES FOR THE DIAGNOSIS AND TREAT-  
MENT OF OSTEOARTHRITIS

(57) Abstract: The invention discloses that members of a subfamily of receptor tyrosine kinases comprising TYRO3, Axl, cMer and ligands thereof, such as GAS6 are suitable targets for the development of new therapeutics to treat, prevent or ameliorate OA. The invention also relates to methods to treat and/or ameliorate OA and pharmaceutical compositions therefor comprising modulators with inhibitory effect on the expression or activity of members of this subfamily of receptor tyrosine and related ligands. The invention also relates to a method to identify compounds with therapeutic usefulness to treat OA, comprising identifying compounds that can, e.g., inhibit activity and/or expression of these polypeptides.

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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP2004/004052

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 G01N33/573 G01N33/566 C12Q1/48

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 G01N C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, Sequence Search

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/081745 A (AVENTIS PHARMA S.A.) 17 October 2002 (2002-10-17) abstract page 46, line 26 - page 48, line 22 claims 1,4,22 SEQ ID NO:230 to 234, SEQ ID NO:158, SEQ ID NO: 172	1-38
Y	O'DONNELL K. ET AL.: "Expression of receptor tyrosine kinase Axl and its ligand Gas6 in rheumatoid arthritis." AM. J. PATHOL., vol. 154, no. 4, April 1999 (1999-04), pages 1171-1180, XP000971169 abstract	1-38
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document but published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*Z\* document member of the same patent family

Date of the actual completion of the international search

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10/01/2005

Name and mailing address of the ISA

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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP2004/004052

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	NAKAMURA Y.S. ET AL.: "Tyro 3 receptor tyrosine kinase and its ligand, Gas6, stimulate the function of osteoclasts." STEM CELLS, vol. 16, 1998, pages 229-238, XP002312139 the whole document	1-38
Y	KATAGIRI M. ET AL.: "Mechanism of stimulation of osteoclastic bone resorption through Gas6/Tyro 3, a receptor tyrosine kinase signaling, in mouse osteoclasts." J. BIOL. CHEM., vol. 276, no. 10, 9 March 2001 (2001-03-09), pages 7376-7382, XP002312140 the whole document	1-38
Y	US 6 096 527 A (GODOWSKI P.J. ET AL.) 1 August 2000 (2000-08-01) abstract column 39, line 10 - line 28 column 42, line 55 - column 43, line 2 example 1 SEQ ID NO:2 is 100% identical to SEQ ID NO: 2 (TYRO 3) in the present application.	1-38
Y	US 5 709 858 A (GODOWSKI P.J. ET AL.) 20 January 1998 (1998-01-20) abstract claims 1-31 SEQ ID NO: 2 is 100% identical to SEQ ID NO: 2 (TYRO 3) in the present application.	1-38
A	EP 0 524 737 A (THE SCRIPPS RESEARCH INSTITUTE) 27 January 1993 (1993-01-27) the whole document	1-38
A	US 5 663 142 A (BONNO N.M. ET AL.) 2 September 1997 (1997-09-02) the whole document	1-38
P,X	WO 2004/029209 A (CENTOCOR, INC.) 8 April 2004 (2004-04-08) the whole document	1-38

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP2004/004052

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 7-38 (in part)  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 7-38 (due to the step of "detecting .... in a biological sample derived from the individual") can be equated to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP2004/004052

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